New Guidelines for Cost-effectiveness Models: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force

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Task Force Leads

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Poll of Audience Background

- Are you familiar with decision modeling used in cost-effectiveness analyses?
  - Yes, I have developed them
  - Yes, I have participated in projects with models
  - Yes, I have read studies that uses them
  - No

For those with experience:

- What types of models are you most familiar with?
  - Decision trees
  - Cohort Markov models
  - Individual-level Markov models
  - Discrete event simulation
  - Other

Background

- ISPOR has good infrastructure for developing best practice papers
    - SMDM has one paper on disaster modeling
- 2003 article in best practices in modeling (Weinstein et al., Value in Health)
- 2010 decision to update that paper with a series of papers and involve SMDM

Working Groups

Conceptual Modeling Working Group

Chair: Mark Roberts; Members: Murray Krahn; David Paltiel; Michael Chambers; Phil McEwan; Louise Russell

State-Transition Modeling Working Group

Chairs: Karen Kuntz; Uwe Siebert; Members: Oguzhan Alagoz; Doug Owens; David Cohen; Beate Jahn; Ahmed Bayoumi,

Modeling Discrete Event Simulation Working Group

Chairs: James Stahl; Jonathan Karnon; Members: Jörgen Möller; Javier Mar; Alan Brennan

Dynamic Transmission Modeling Working Group

Chairs: Richard Pitman; John Edmunds; Members: Maarten Postma; Greg Zaric; Marc Brisson; David Fisman; Mirjam Kretzschmar

Model Parameter Estimation & Uncertainty Working Group

Chair: Andrew Briggs; Members: Milt Weinstein; Mark Sculpher; Elisabeth Fenwick; David Paltiel; Jonathan Karnon

Model Transparency and Validation Working Group

Chairs: David Eddy; John Wong; Members: Joel Tsevat; William Hollingworth; Kathy McDonald

Published Papers

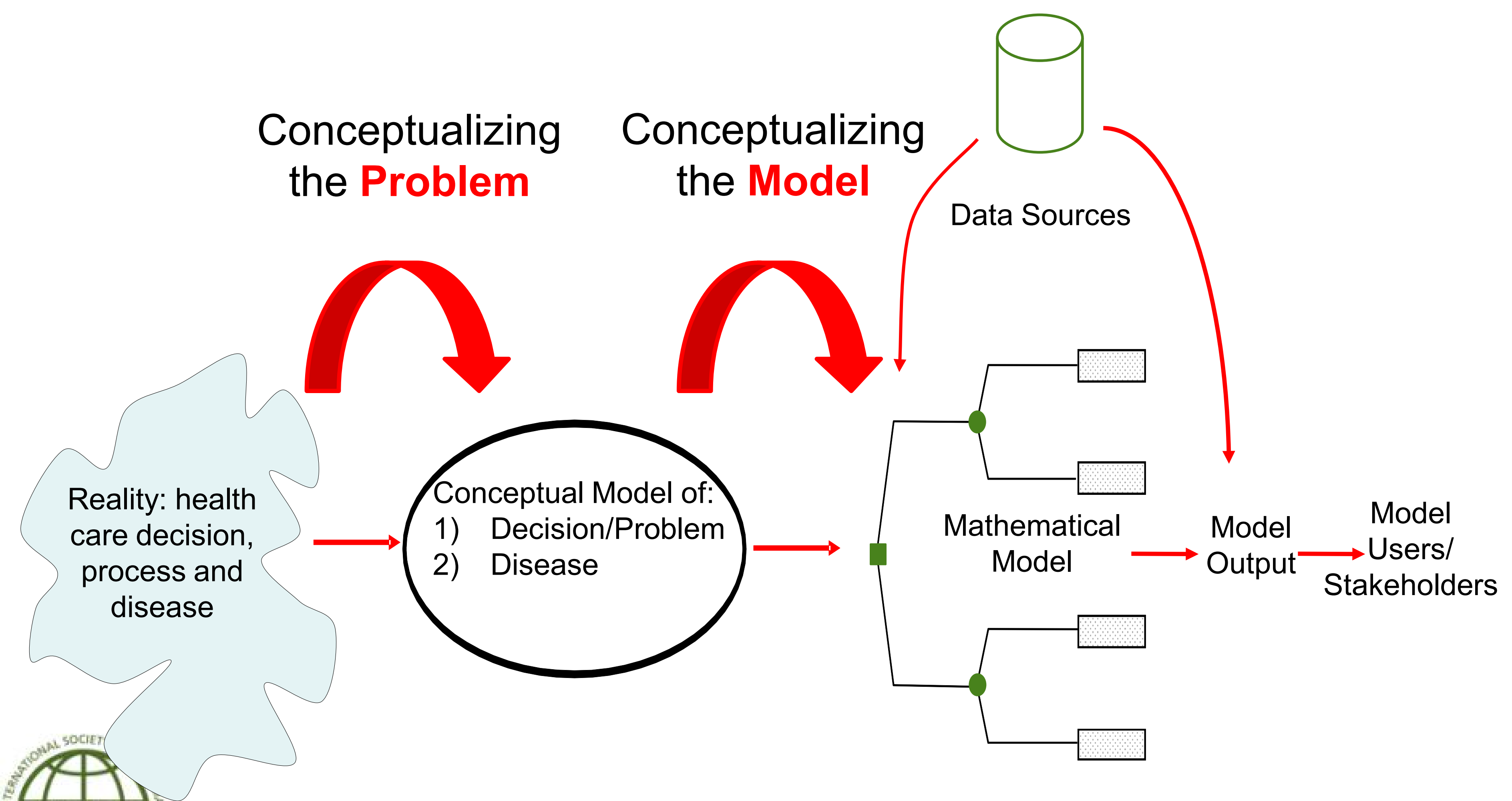
- Seven papers – one from each working group and an overview paper
- *Medical Decision Making* 2012 Sept-Oct Issue
- *Value in Health* 2012 September Issue

Review Process

- All papers underwent external review
  - Broad representation
  - Reviewed/approved by journal editors
  - Peer review comments documented as well as responses
- Papers posted for members' review & comment
- Submission jointly to MDM & ViH
- Editors review

Conceptualizing the model

Conceptual Framework



Conceptualizing the Model

- **Collaborate and consult** to ensure that model adequately addresses decision problem & disease in question
- Clear, written **statement of the decision problem**, objective and scope
- **Conceptual structure** should
  - Be linked to the problem and **not based on data availability**
  - Be **used to identify key uncertainties in model structure** where sensitivity analyses could inform the impact of structural choices
  - Follow an explicit process to convert the conceptualization into an appropriate model structure: Influence diagrams, concept mapping, expert consultations
- Model **simplicity is desirable** for transparency, ease of validation and description, but
  - Must be **sufficiently complex to answer the question**
  - Should **maintain face validity**

Choice of Model Type

Problem Characteristic	Model Type
Simple, non-dynamic	Decision tree
Based on "states" of health	State transition model
State explosion	Individual microsimulation
Interactions, event-based, time-to-event	Dynamic transmission models, DES, agent-based
Resource constraints, interactions	DES, agent-based, dynamic transition models

For some decision problems, combinations of model types, hybrid models, and other modeling methodologies are appropriate

Uncertainty

- All modeling studies **should include an assessment of uncertainty** as it pertains to the decision problem
- **Role of decision maker** should be considered
- Authors should be aware that **terminology varies** within the decision modeling & related fields
  - carefully define terminology to avoid confusion
- Identify & incorporate **all relevant evidence**, rather than cherry-picking the "best" source
- Whether employing deterministic SA methods (point estimate & range) or probabilistic SA (parameterized distribution) the **link to the underlying evidence base should be clear**

Terminology

Preferred term	Concept	Other terms sometimes employed	Analogous concept in regression
First-order uncertainty	Random variability in outcomes between identical patients	• Variability • Monte Carlo error • Unexplained heterogeneity	Error term
Parameter uncertainty	The uncertainty in estimation of the parameter of interest	• Second-order uncertainty	Standard error of the estimate
Heterogeneity	The variability between patients that can be attributed to characteristics of those patients	• Variability • Observed or explained heterogeneity	The Beta coefficients (or variability of fitted dependent variable)
Structural uncertainty	The assumptions inherent in the presentation of the decision modeling form	• Model uncertainty	The form of the regression model (linear/log-linear etc.)

Parameter estimation & uncertainty

Estimating Parameters

- While completely **arbitrary analyses** (e.g., varying an input parameter by +/- 50%) can be used as a measure of sensitivity, they **should not be used to represent uncertainty**
- Consider using **commonly adopted standards from statistics**, such as 95% confidence intervals, or distributions based on agreed statistical methods for a given estimation problem
- Where there is very little information, **analysts should adopt a conservative approach**
- In choosing distributional forms for parameters in a probabilistic sensitivity analysis, favor should be given to continuous **distributions that provide a realistic portrayal of uncertainty** over the theoretical range of the parameter of interest
- **Correlation** among parameters should be considered

Structural Uncertainty

- Where **uncertainties in structural assumptions** were identified in the process of conceptualizing and building a model, those assumptions **should be tested in a sensitivity analysis**
  - Consideration should be given to opportunities to **parameterize these uncertainties** for ease of testing
  - Where it is not possible to perform structural sensitivity analysis it is nevertheless important that analysts be aware of the **potential for this form of uncertainty to be at least as important as parameter uncertainty** for the decision maker

Reporting Uncertainty

- Uncertainty analyses can be **deterministic or probabilistic**
  - often appropriate to report aspects of both
- When **additional assumptions or parameter values** are introduced **for** purposes of **uncertainty analyses**, these values **should be disclosed & justified**
- When model calibration is used to derive parameters, **uncertainty around the calibrated values** should also be reported, & this uncertainty should be reflected
- When the purpose of a probabilistic sensitivity analysis is to guide decisions about acquisition of information to reduce uncertainty, results should be presented in terms of expected **value of information**
- When more than two comparators are involved, **CEACs for each comparator should be plotted on the same graph**

Dynamic Transmission Models

Dynamic Transmission Models

- What are they:
  - Models where the risk of infection is dependent on the number of infectious agents at a given point in time
- When to use:
  - When evaluating an intervention for an infectious disease that

    1) has an impact on disease transmission in the population, and/or

    2) alters the frequency distribution of strains (e.g., genotypes or serotypes)
- Use appropriate type based on complexity of the interactions, size of the population, and role of chance
  - Can be deterministic or stochastic, cohort or individual
  - Justification for the model structure should be given

Agent-based Models

- If using an agent-based model, thoroughly describe
  - the rules governing the agents,
  - the input parameter values,
  - initial conditions and all
  - sub-models

State-Transition Models

Structure

- Cohort or individual simulation?
  - **<u>Cohort</u>**: if the decision problem can be represented with a **<u>manageable number of health states</u>** incorporating all characteristics relevant to the decision problem
  - **<u>Individual</u>**: if **<u>unmanageable number of states</u>**
- **<u>Validity should not be sacrificed for simplicity</u>**
- Specification of **<u>states and transitions should</u>** **<u>reflect</u>** the biological/theoretical understanding of the **<u>disease</u>** or condition being modeled
- **<u>States need to be homogeneous</u>** with respect to the observed and unobserved (i.e., not known by the decision maker) characteristics that affect transition probabilities
- **<u>Cycle length</u>** should be **<u>short enough to represent</u>** the frequency of clinical events and interventions

Parameters

- **Parameters** relating to the intervention effectiveness **derived from observational studies** should be correctly **controlled for confounding**
  - Time-varying confounding is of particular concern in estimating intervention effects

Reporting

- Communicate **key structural elements**, **assumptions** and **parameters** using nontechnical language and clear figures that enhance understanding of the model
- Depending on the problem, report **not only** the **expected value** but **also the distribution** of the outcomes of interest.
- In addition to final outcomes, **intermediate outcomes should be presented** that enhance understanding and transparency of the results
- Paper contains illustrative examples of both cohort & microsimulation

Discrete Event Simulation

Areas of Application

- Constrained resource scenarios
  - Optimising the delivery of services
  - technologies result in differing levels of access (e.g. different referral rates) and
  - time to access resources can have significant effects on costs and/or outcomes
- Non-constrained resource scenarios
  - More complex health technology assessments
  - An alternative to individual state-transition models
    - Provides additional flexibility in representing time

Structure

- To simplify debugging and updating, sub-models should be used
- If downstream decisions can have significant effects on costs or outcomes, structure should facilitate analyses of alternative downstream decisions
- Mechanism for applying ongoing risks should remain active over the relevant time horizon
- For structural sensitivity analyses, alternative structures should be implemented within a single DES

Parameterisation

- With competing risks, parameterisation approaches that represent correlations between the competing events are preferred
  - Rather than specifying separate time to event curves for each event.
- Where possible, progression of continuous disease parameters and the likelihood of related events should be defined jointly
  - e.g., sample the level of the continuous measure at which an event occurs, then sample the time at which the level is reached

Implementation

- Software choice depends on importance of flexibility & execution speed (general programming) vs. efficiency
  - Spreadsheet software is inappropriate for implementing DES
- Outputs should
  - be stored as attributes only when individual outcomes are required, otherwise aggregated values should be collected from each run
  - account for the outputs required for validation
- When run times are constrained,
  - optimal combination of run size & numbers of alternative input parameter sets tested should be estimated empirically
    - variance reduction techniques should be implemented
  - factorial design and optimum seeking approaches can be used
  - meta-modelling can be used
- If system is not empty at start, use a warm-up period if:
  - it can be assumed that the key parameters have remained constant over time
  - history of the key parameters can be incorporated into the warm-up period

Reporting

- Animated representation that displays the experience of events by individuals is recommended as a means of engaging with users, as well to helping to debug the model through the identification of illogical movements
- Both general and detailed representations of a DES model's structure and logic should be reported to cover the needs of alternative users of the model

Transparency & Validation

Transparency

- Every model should have **non-technical documentation** that should
  - Be **freely accessible** to any interested reader
  - Describe in non-technical terms the type of model and intended applications; funding sources; structure of the model; inputs, outputs, other components that determine the model's function, and their relationships; data sources; validation methods and results; and limitations.
- Every model should have **technical documentation** that should
  - Be made available at the discretion of the modelers either **openly or under agreements that protect intellectual property**
  - written in sufficient detail to enable a reader with the necessary expertise to evaluate the model and potentially reproduce it
- Modelers should **identify parts** of a model **that couldn't be validated** because of lack of suitable data sources, and describe how uncertainty about those parts is addressed.
- For multi-application models, **describe criteria for** determining when validations should be repeated and/or expanded.

Validation

- **Face validity** of structure, evidence, problem formulation, and results
  - Should be made by people who have **expertise** in the problem area, but are **impartial** to the results
  - **Process** used should be **described**
  - If **questions** about the model arise, these issues should be **discussed**
- Verification (internal validity/consistency)
  - Should be **described** in the non-technical documentation
  - Results should be **made available on request**
- Published models of same or similar problems should be sought and similarities and differences discussed

External Validation

- Formal process for conducting external validation that includes:
  - Systematic identification & justification of data sources
  - Specification of whether a data source is
    - dependent,
    - partially dependent, or
    - independent;
  - Description of which parts of the model are evaluated by each
  - Simulation of each data source and comparison of results
  - Measures of how results match observed outcomes
- Description of external validation & results available on request
- When feasible, test for prediction of future events
- Seek opportunities to conduct predictive validations as part of the overall validation process

Final Poll

- Which of the following recommendations do you agree with least?
  - Structure linked to problem and not based on data availability
  - Model simplicity is desirable
  - Varying inputs arbitrarily does not represent uncertainty
  - Technical documentation should be detailed enough to reproduce model
  - I agree will all of them